REMARKS

The present Amendment is in response to the Examiner's Office Action mailed on January 23, 2004. Claims 17, 22, 24 and 26-53 have been cancelled. Claim 1 has been amended. Claims 1-16, 18-21, 23 and 25 are pending.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remakes are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 1-20, 23, and 25 under 35 U.S.C. §112, second paragraph as being indefinite.

In response, as suggested by the Examiner, Applicants amend claim 1 to specify "a method of treating cancer in a cancer patient". Applicants also cancel claim 17. In view of these amendments to the claims, Applicants respectfully request the Examiner to withdraw this ground of rejection.

II. Rejection Under 35 U.S.C. § 103(a)

The Examiner rejects claims 1-21, 23, and 25 under 35 U.S.C. §103(a) as being unpatentable over Rubinfeld (US Patent No: 6,191,119) in view of Achterrath (US Patent No: 6,403,569).

Independent claim 1 as amended specifies a method for treating cancer in a patient by using a sequential therapy of a **water-insoluble** 20(S) camptothecin (e.g., 9-nitro-20(S)-camptothecin (9NC) or 9-amino-20(S)-camptothecin (9AC)) and 5-fluorouracil (5-FU). According to the method, 9NC or 9AC is administered to the patient at least 1 day before or after administration of 5FU. During this time period, 5-FU is not present in the patient in a pharmaceutically active form. Support for the claim language appears in the Specification, for example, at page 6, lines 9-17. According to Giovanella et al. (U.S. Patent No. 5,552,154,

Column 3, lines 32-60) and as described in the Specification at page 3, lines 9-11, 9NC and 9AC are **water insoluble** camptothecin derivatives.

In contrast, Rubinfeld discloses using 20(S)-camptothecin in combination with other therapeutics in general. As acknowledged by the Examiner, Rubinfeld discloses that 20(S)-camptothecin and the other therapeutics can be co-administered during overlapping periods of time. This reference neither teaches administering 9NC or 9AC to a cancer patient at least 1 day before or after administration of 5-FU, nor suggests that such a water insoluble campthecin compound should be administered while 5-FU is not present in a pharmaceutically active form in the body.

On the other hand, Achterrath merely teaches a combination therapy of camptothecin (e.g., CPT-11), 5-fluorouracil (5-FU), and folinic acid (FA). As showed in Exhibit A which is a copy of a section of "Current Cancer Therapeutics", 3rd Ed., Kirkwood et al., pp. 118-119 (1998) CPT-11 (also called irinotecan) is a **water soluble** camptothein derivative. This drug is dissolved in infusion fluid and administered to a patient via IV infusion over 90 min. *See* page 118 under "Dosage and Administration".

Accordingly, Achterrath combined the water soluble campthecin derivative CPT-11 with the other two drugs and administered them by infusion weekly, or in by following the de Gramont treatment schedule in which the combination is administered in two-week intervals. Column 3, lines 49-62. The combination of CPT-11 and 5-FU is administered within a 24-hr time period. For example, Achterrath teaches that

> **On day 1,** FA 200 mg/m^2 i.v. was administered over **2 hours followed by** the administration of 400 mg/m^2 5-FU i.v. bolus and 600 mg/m^2 5-FU i.v. over **22 hours** (one cycle) and administration of 180 mg/m^2 CPT-11 i.v. **On day 2,** 200 mg/m^2 i.v. of FA was administered over 2 hours.

Column 5, lines 23-28. Emphasis Added. Thus, Achterrath fails to teach the claimed sequential therapy which involves administering a water insoluble camptothecin compound at least 1 day before or after the administration of 5-FU.

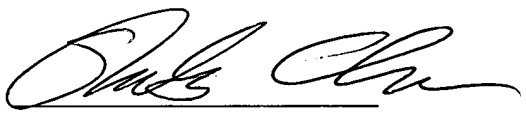
In view of the distinct chemical, physical and pharmacokinetic differences between a water soluble camptothecin derivative (e.g., CPT-11) and a water insoluble camptothecin derivative (e.g., 9NC or 9AC) and the lack of guidance in the cited references as to the specific treatment regimen of a sequential administration of 9NC (9AC) and 5-FU, one of ordinary skill

in the art would not be motivated by the general teaching of Rubinfeld et al. to modify Achterrath to arrive at the claimed invention. Thus, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

CONCLUSION

Applicants believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent to issuance. Should the Examiner have any questions, Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: April 19, 2004 By: 

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